

**REMARKS**

Applicants respectfully request reconsideration of this application and the Official Action dated February 12, 2003.

A request for a three (3) month extension of time and associated fee is filed herewith.

The Office Action indicates that the priority document has not been filed. Applicants did, in fact, file the priority document on April 18, 2001, as shown by the enclosed photocopy of counsel's postcard receipt date stamped by the PTO. Applicants therefore request a search of the PTO records be carried out to locate the missing document.

The claims in the application are Claims 33 to 97, with Claims 42-54, 60, 61, 63, 68, 69, 72, 75-87 and 90-97 being withdrawn from further consideration. The non-elected claims have been identified in the Official Action and applicants reserve the right to file such divisional applications as may be necessary to adequately the subject matter of this invention.

Applicants note the entry of a double-patenting rejection in connection with Claims 33-41, 55-59, 62, 64-67 and 70, and respectfully request that this matter be deferred until an indication of allowable subject matter in either the related application, Serial No. 09/519,918 (Docket No. 033700WN003), or in the above-identified application.

Claims 33-41, 55-59, 62, 64-67, 70, 73-74, 88 and 89 stand rejected under 35 U.S.C. § 112 second paragraph as being indefinite. Applicants traverse this rejection and request reconsideration in view of the amendment presented herein.

The Official Action asserts that the phrase "a derivative, mutant or fragment of avidin" and the phrase "a derivative, mutant or fragment of streptavidin" in Claim 33 is vague and

indefinite. In response, applicants have amended Claim 33 to specify that the respective member includes a derivative of avidin or a derivative of streptavidin and applicants submit that with this amendment the claims do not contain any terms which one skilled in the art would not be apprised of or understand.

The term "capable of" has been replaced in Claim 33 by specifying that the enzyme is present which optionally is for converting a pro-drug to an active drug. It is believed that with this terminology, the rejection set forth in the Official Action has been overcome.

The term "groups of atoms" has been deleted in Claims 55, 56, 64 and 65, thereby rendering the objection under 35 U.S.C. § 112 moot.

With respect to the term "active ester" in Claim 62, reference is made to the application on page 15, lines 5-10, which define this term. It is a conventional term for esters which easily react with electrophilic substances.

Claim 70 has been amended to remove the formality as to the missing period in the claim by adding the phrase "wherein such member is stabilized against enzymatic cleavage in linker 1".

With regard to the term "derivative", Claim 33 specifies that the derivative of avidin or streptavidin has essentially the same binding function to the affinity ligand. Therefore, the term "derivative" does not encompass an enumerable number of chemicals, but instead constitutes derivatives which are known to ordinary skill in the art and have essentially the binding function to the affinity ligand as to avidin or streptavidin.

With regard to Claims 88 and 89, which have been indicated in the Office Action as being vague and indefinite, as well as confusing, applicants point out that Claims 88 and 89 have been amended to remove the terms "optionally modified" and "having a desired biological property retained". With respect to the expression "having at least one affinity ligand and at least one effector agent bound to the reagent" which appears in these claims, this can be explained by the fact that the trifunctional linking entity optionally may be tetrafunctional as stated in present Claim 33. In view of the foregoing, applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112 be reconsidered and withdrawn.

The rejection of Claims 33-35, 39-41, 55-59, 62, 64-67, 73-74, 88 and 89, under 35 U.S.C. § 102(b) as anticipated by the *Wilbur* International Publication WO 97/29114 is traversed and reconsideration is respectfully requested. With the amendment of Claim 33 as set forth herein, applicants respectfully submit that the *Wilbur* patent does not show a first linker stabilized to inhibit enzymatic cleavage of the affinity ligand.

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*Wilbur* neither discloses nor describes a reagent that includes three essential components as recited in the present invention; namely, an affinity label, an effector and a biomolecule reactive moiety that is also designed to be protected against biotinidase. Hence, *Wilbur* fails as a reference under 35 U.S.C. § 102(b).

Applicants' invention provides a reagent having three different moieties (an affinity label, an effector, and a biomolecule reactive moiety) each serving a specific need of simultaneously labeling of targeting molecules for in vivo diagnostic and therapeutic applications in conjunction with extracorporeal removal of non-targeted molecules from blood circulation.

Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

The rejection of Claims 36-38 and 70 under 35 U.S.C. § 103(a), as unpatentable over *Wilbur*, taken with *Griffiths* (US 5,482,698) is traversed and reconsideration is respectfully requested. *Wilbur* is discussed above and the comments made apply here as well. In addition, it is to be noted that *Wilbur* fails to contain any reason, suggestion or motivation for a person skilled in the art to arrive at applicants' invention. The secondary reference of *Griffiths* is said to teach detection and therapy of lesions with biotin/avidin polymer conjugates.

*Griffiths* does not, by itself, teach anything related to the present invention but describes various means for pre-targeting of cell toxic agents with the aim of further accumulating cell toxic agents to the tumor cells. The *Griffiths* document fails to provide any motivation for a person skilled in the art to arrive at the present invention. A person skilled in the art would not be lead to combine *Wilbur* and *Griffiths* with a view to solving the problems-as-discussed-in the present invention and achieve a successful solution to that problem.

Applicants respectfully submit that the combination of references would not lead a person skilled in the art to use biotin as homobiotin with the expectation of achieving reversible binding.

To establish a *prima facie* obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure, *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916837 F2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

A statement that the modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* obviousness without

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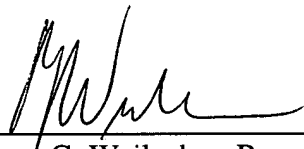
some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ 2d, 1300 (Bd. Pat. App. & Int. 1993).

For the reasons set forth above, applicants respectfully submit that the rejection fails to establish *prima facie* obviousness for the claimed invention.

Favorable action at the Examiner's earliest convenience is respectfully requested.

Respectfully submitted,

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